UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/555,780	11/17/2000	Helene Gras-Masse	1091/2 PCT/US	9478

7590 03/22/2006

Irving N Feit
Hoffmann & Baron
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
SALVOZA, M FRANCO G	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 03/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/555,780
Filing Date: November 17, 2000
Appellant(s): GRAS-MASSE ET AL.

Edna I. Gergel, Ph.D.

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 12/12/05 appealing from the Office action mailed 04/07/05.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

Appellant's brief presents arguments relating to objections to claim 5. This issue relates to petitionable subject matter under 37 CFR 1.181 and not to appealable subject matter. See MPEP § 1002 and § 1201.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Stuhler et al., "Antigen organization regulates cluster formation and induction of cytotoxic T lymphocytes by helper T cell subsets," *Proc. Natl. Acad. Sci.*, 94:622-627 (1997).

Sastry et al., "Identification of T-cell epitopes without B-cell activity in the first and second conserved regions of the HIV Env protein," *AIDS*, 5:699-707, (1991).

Sugimoto et al. (J. Immunol. 1978, 120:980-982, abstract only).

Kramer et al., EP0230222 (1987).

Shapiro et al., "Stabilization of the peptide conformation on the micellar surface," *Analyst*, 119(4): 647-52 (1994).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-7, 9-10, 15, 17-19 and 21-24 were rejected under 103(a) for being obvious over Stuhler et al., Sastry et al., and Sugimoto et al.

Claim 1 is drawn to a composition of mixed micelles for inducing an immune response comprising micelles or microaggregates wherein each micelle comprises more than one first lipopeptide comprising a CTL antigenic determinant and at least one lipid unit and a second lipopeptide comprising at least one helper T antigenic determinant and at least one lipid unit.

Claims 2-6 recite further limitations of the lipid units of the micelle that are met by the embodiment of palmitic acid residues recited in Sastry et al.: the first and second lipopeptides each comprise one or more C4-C18 lipid units (claim 2); the first and second each comprise one or two C4-C18 lipid chains linked by a covalent bond to one or two amino acids of the respective lipopeptide (claim 3); the lipid units each comprise two palmitic acid chains linked to a lysine through an NH2 group of said lysine (claim 4); the specific embodiment of a residue of palmitic acid (claim 5); the nonlipid part of each of the first and second lipopeptides comprises between 10 and 100 amino acids (claim 6). Thus, each of claim 2-5 requires the presence of one or two palmitic acids (a C4-C18 lipid chain).

Claims 10 and 15 recite further limitations met by the HIV proteins and pharmaceutical compositions recited in both Stuhler et al. and Sastry et al.

Claims 7 and 9 recite further limitations of the helper T antigenic determinant: multivalency (claim 7); comprising the antigenic determinant of hemagglutinin (HA) or the PADRE antigenic determinant (claim 9). Finally, claims 17-19, 21-24 recite a method for producing the micelles or micro-aggregates and a method for inducing an immune response.

Stuhler et al. teaches a critical linkage of epitopes for helper T antigenic and CTL antigenic determinants (see the abstract and introduction, p. 622). Stuhler et al. were able to activate a more complete immune response by using helper T and CTL antigenic determinants, in this reference by using HIV gag peptide as the CTL epitope and keyhole limpet hemocyanin (KLH) as a helper T epitope (see the "Materials and Methods" and the "Results" sections, pp. 622-623). Thus, the reference teaches a composition for inducing an immune response comprising at least one CTL antigenic determinant, and at least one helper T antigenic determinant.

Stuhler et al. does not teach conjugating the CTL epitope and the helper T epitope in a micelle composition with palmitic acid residues, or the composition comprising micelles wherein each micelle comprises more than one first lipopeptide comprising at least one CTL antigenic determinant and at least one lipid unit and a second lipopeptide comprising at least one helper T antigenic determinant and at least one lipid unit recited in claim 1.

However, Sastry et al. teaches a method of eliciting cell-mediated immunity with micelle compositions. These compositions comprise short peptide sequences of HIV envelope protein gp 160 (a CTL determinant) with two palmitic residues (or lipid units) attached to the amino-

terminal lysine, or what is recited claim 1 - more than one first lipopeptide comprising at least one CTL antigenic determinant and at least one lipid unit. More specifically, Sastry et al. teaches "peptide sequences (plural, "Peptide synthesis," p. 700) and "lipid micelle polymers formed by attaching an amino-terminal lysine to the peptide sequence in question and then coupling a fatty acid (lipid unit) to both the alpha and epsilon amino groups" (p. 700). In other words, the reference teaches lipid micelle polymers of the peptide sequence with at least one CTL determinant in question with more than one lipid unit.

Sastry et al. also indicates that the use of peptides in micelle configurations is a commonly-known, accepted and even encouraged technique known in the art for inducing effective immune responses: "Peptides were chemically modified to form polymers or micelles. This technique, though not a new one, is an essential procedure for using synthetic peptides as vaccine candidates" (p. 706). Sastry et al. also teaches micelle polymers with helper T antigenic determinants and more than one CTL determinant (see pages 701 ("Table 1") and 704 ("Discussion")).

One of ordinary skill in the art at the time the invention was made would have been motivated to combine the method of Stuhler et al. using both a CTL and helper T determinant in the micelle composition of Sastry et al. because Stuhler et al. teaches that a linkage of CTL and helper T determinants results in successful stimulation of a more complete immune response. More specifically, Stuhler et al. teaches that the organized linkage of CTL and helper T antigenic determinants more efficiently creates a tight cluster on one antigen presenting cell (APC), resulting in more specifically regulated immune responses (p. 626). Furthermore, Sastry et al.

teaches a method of successfully stimulating an immune response to HIV envelope protein (a CTL determinant) by using the protein in a micelle configuration with palmitic acid residues.

Therefore, one would have motivated to combine the CTL and helper T antigenic determinants of Stuhler et al. with the CTL antigenic determinant in a micelle configuration with palmitic acid residues of Sastry et al. to improve specificity and regulation of immune response.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in producing the claimed composition and specific immune response because Stuhler et al. and Sastry et al. both teach the stimulation of immune response using a combination of helper T and CTL antigenic determinants. Since Stuhler et al. teaches the linkage of helper T epitopes to CTL epitopes elicited a more complete immune response, one would reasonably expect the linkage of helper T epitopes to the CTL epitope and palmitic acid residues in micelle configuration in Sastry et al. to also successfully elicit a more complete response.

Therefore, the invention as a whole would have been prima facie obvious at the time the invention was made.

With respect to claim 9, it is also noted that Stuhler et al. does not teach using hemagglutinin (HA) as a helper epitope. However, it is well known in the art that keyhole limpet hemocyanin (KLH) can be substituted by HA because of similarity in immune response achieved with both, indicating functional equivalency (see the abstract of Sugimoto et al. as evidence; see also MPEP section 2144.06 for functional equivalency).

Claim 11 stands rejected under 103(a) over Stuhler et al., Sastry et al., and Sugimoto et al., and further in view of Kramer et al.

Claim 11 further limits the composition according to claim 1 to an embodiment wherein said micelle comprises the lipopeptide SEQ ID NO: 6.

See the teachings of Stuhler et al., Sastry et al., Sugimoto et al. above. Neither Stuhler et al., nor Sastry et al., nor Sugimoto et al. teaches gag 253 sequence of SEQ ID NO: 6.

Kramer et al. teaches the sequence and that it is immunogenic and can be used in detection assays and pharmaceutical compositions (see the sequence alignment provided by the Geneseq database and the excerpt provided with the alignment).

One of ordinary skill in the art at the time the invention was made would have been motivated to use this protein for the immunogenic properties taught by Kramer et al.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in using this peptide in the method of generating a simultaneous three-way immune response taught by Stuhler et al. because Sastry et al. teaches that micelle compositions is the preferred technique for using synthetic peptides in vaccine compositions.

Therefore, the invention as a whole would have been prima facie obvious at the time the invention was made.

Claim 18 was rejected under 103(a) over Stuhler et al., Sastry et al., Sugimoto et al., Kramer et al., and further in view of Shapiro et al.

Claim 18 recites the method of claim 17 wherein the dispersing of the lipopeptides dissolved in acetic acid is confirmed by a two-dimensional nuclear magnetic resonance method.

The combination of Stuhler et al., Sastry et al., Sugimoto et al., Kramer et al. teach a composition for inducing an immune response comprising micelles wherein each micelle comprises more than one first lipopeptide comprising at least one CTL antigenic determinant and at least one lipid unit, and a second lipid lipopeptide comprising at least one helper T antigenic determinant and at least one lipid unit, wherein embodiments include hemagglutinin as the helper T determinant and the micelles comprise as a lipopeptide SEQ ID NO:6. Sastry et al. also teaches that the micelles are dissolved in a solution of acetic acid (p. 700). Neither Stuhler et al., nor Sastry et al., Sugimoto et al., nor Kramer et al. teaches the use of nuclear magnetic resonance (NMR) in the preparation of micelle compositions.

Shapiro et al. teaches the use of two-dimensional nuclear magnetic resonance (NMR) to aid in analyzing the conformation of micelle/peptide-receptor interactions.

One of ordinary skill in the art at the time the invention was made would have been motivated to utilize two-dimensional nuclear magnetic resonance (NMR) to analyze and confirm the interaction between the targeted APC and the micelle since Shapiro teaches the use of NMR as a widely known, accurate, and specific method to analyze the micelles and study the peptide conformations and their interactions at the receptor level.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for success of producing the claimed invention because conformational data from NMR can be readily analyzed from the data from the CTL/helper T epitope sequences

taught by Kramer et al. and Sugimoto et al. and the receptors on the APC surface used to stimulate the three-way immune cluster taught by Stuhler et al.

Therefore, one of ordinary skill in the art would have had a reasonable expectation to use the method to analyze the micelles suggested by the previously cited references.

Therefore, the invention as a whole would have been prima facie obvious at the time the invention was made.

(10) Response to Argument

Claims 1-7, 9-10, 15, 17-19, and 21-24 stand rejected under 35 U.S.C. 103(a) over Stuhler et al., Sastry et al., and Sugimoto et al. Claim 11 stands rejected under 35 U.S.C. 103(a) over Stuhler et al., Sastry et al., and Sugimoto et al. and further in view of Kramer et al. Claim 18 stands rejected under 35 U.S.C. 103(a) over Stuhler et al., Sastry et al., Sugimoto et al., Kramer et al., and further in view of Shapiro et al.

Appellant has provided four main arguments in traversal of the rejection, none of which should be found persuasive for the reasons cited below.

1. Sastry et al. does not teach away from the use of helper T determinants in a composition such as described in claims 1-7, 9-10, 15, 17-19, and 21-24.

The Appellant's first argument in traversal of the rejection is:

The purpose of the experiments in Sastry et al. is to obtain a cytotoxic immune response without antibody production or the identification of potential T lymphocyte antigenic determinants without B cell activity.

This argument should not be found persuasive.

First, the obviousness rejection at present under 103(a) involves *a combination* (emphasis added) of references including Sastry et al. but not Sastry et al. exclusively to teach the lipid polymer micelles to induce an immune response.

Second, Stuhler et al. teaches that helper T cell response is required for CTL responses (p. 622, right column), and that HTL response are involved in either cellular (T-cell) or humoral (B-cell or antibody) responses. Id. Thus, Stuhler et al. supports Appellant's assertion that helper T responses are required for B-cell responses. However, Stuhler et al. also teaches that they are - independently - also involved in CTL response. Therefore, Stuhler et al. does not support the Appellant's assertion that HTL responses necessarily give rise to antibody responses, and, thus, Sastry et al. does not teach away from the use of helper T determinants.

Therefore, the rejection should be affirmed over this argument in traversal.

2. There is a suggestion or motivation to combine Stuhler et al. and Sastry et al.

The Appellant's second argument in traversal of the rejection is:

There is a lack of motivation to combine the references because Sastry et al. wished to obtain a good CTL response without antibody production, while Stuhler et al. suggest that a good

cytotoxic immune response requires the production of antibodies. Therefore, the two references constitute divergent teachings.

This argument should not be found persuasive.

The teachings of Sastry et al. as set forth previously in the **Grounds of Rejection** as well as more recently in Response to Argument 1 demonstrate that Applicant's arguments with respect to Sastry et al. are insufficient due to the fact that the rejection is based upon a combination of references. The elements missing from Sastry et al. are taught by the other references.

Based on the teachings of the references as set forth above (see **Grounds of Rejection**), one of ordinary skill in the art would have a suggestion or motivation to combine the method of Stuhler et al. using both a CTL and helper T determinant in the micelle composition of Sastry et al. because Stuhler et al. teaches that a linkage of CTL and helper T determinants results in successful stimulation of a more complete immune response. More specifically, Stuhler et al. teaches that the organized linkage of CTL and helper T antigenic determinants more efficiently creates a tight cluster on one antigen presenting cell (APC), resulting in more specifically regulated immune responses (p. 626). Furthermore, Sastry et al. teaches a method of successfully stimulating an immune response to HIV protein by using the protein in a micelle configuration with palmitic acid residues.

Therefore, one would have been motivated to combine the CTL and helper T antigenic determinants of Stuhler et al. with the CTL antigenic determinant in a micelle configuration with palmitic acid residues of Sastry et al. to improve specificity and regulation of immune response.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in producing the claimed composition because Stuhler et al. and Sastry et al. both teach the stimulation of immune response using a combination of helper T and CTL antigenic determinants. Since the linkage of helper T epitope to CTL epitope in Stuhler et al. elicited a more complete immune response, one would reasonably expect the linkage of helper T epitope to the CTL epitope and palmitic acid residues in micelle configuration in Sastry et al. to successfully elicit a more complete response as well. Because these references are directed to the induction of a CTL response, they suggest a composition to induce an immune response as required by the claims.

Therefore, the invention as a whole would have been prima facie obvious at the time the invention was made.

Contrary to Appellant's assertion, Stuhler et al. does not require an antibody response. Stuhler et al. teaches that helper T cell response is required for CTL responses (p. 622, right column), and that different types of helper T cell responses are involved in either cellular (T-cell) or humoral (B-cell or antibody) responses. Id. Thus, the reference teaches that a helper T cell response is involved with both types of responses, but nowhere teaches that there is a requirement for an antibody response in eliciting a CTL response.

Therefore, one would have been motivated to combine the method of Stuhler et al. using both a CTL and helper T determinant in the micelle composition of Sastry et al. because Stuhler . teaches that a linkage of CTL and helper T determinants results in successful stimulation of a more complete immune response. Additionally, both Stuhler et al. and Sastry et al. teach the stimulation of CTL responses. So the teachings are not divergent as Appellant suggests, rather,

they are quite compatible teachings and further, one would have been motivated to combine them for the reasons cited.

Thus, the rejection should be affirmed over this argument in traversal.

3. Sugimoto et al. is material to patentability.

The Appellant's third argument in traversal of the rejection is:

Appellant argues that the Sugimoto et al. reference is not relevant or material to the obviousness rejection of claim 1, which is not limited to a particular T helper antigenic determinant. Instead, only claim 9 recites hemagglutinin.

This argument should not be found persuasive.

The teachings of Sugimoto et al. are not relied on to teach the limitations of claim 1 as demonstrated above (**Grounds of Rejection**). However, the teachings of the reference are relevant to the invention of claim 9, which represents an embodiment of the invention of claim 1. Thus, while the reference may not be required for the rejection of claim 1, it is relevant to the rejection of the claims in general.

4. The combination of Stuhler et al., Sastry et al., and Sugimoto et al. teach or suggest all the claim elements.

The Appellant's fourth argument in traversal of the rejection is:

The cited references do not disclose or suggest a composition as presently claimed, since Sastry et al. teaches only multiple copies of a single peptide sequence, and not more than one first lipopeptide as recited in claim 1.

This argument should not be found persuasive.

Claim 1 recites a composition for inducing an immune response comprising micelles (or micro-aggregates) wherein each micelle or micro-aggregate comprises more than one first lipopeptide comprising at least one CTL antigenic determinant and at least one lipid unit, and a second lipopeptide comprising at least one helper T antigenic determinant and at least one lipid unit.

Sastry et al. teaches more than one lipopeptide comprising at least one CTL antigenic determinant and at least one lipid unit.

First, Sastry et al. teaches the use of "peptides," plural, or "at least one CTL antigenic determinant." Sastry et al. states: "We have selected a total of 19 synthetic peptides from the envelope protein of gp160 representing the first and second conserved regions (peptides 103-112 and 113-117 respectively) and three functionally important segments (peptides 61, 63, 65 and 67)" (p. 701). Although they are all derived from a single gp160 protein from HIV, the derived peptides teach distinct epitopes and "at least one CTL determinant," as recited in claim 1. The amino acid sequences are listed in Table 1 (p. 701).

Sastry et al. also teaches more than one lipopeptide comprising at least one CTL antigenic determinant and at least one lipid unit, as further recited in claim 1.

In the section subtitled, "Peptide polymers" (p. 700), Sastry et al., states: "Two types of polymers were prepared: (1) double cysteine polymers linked end to end by disulfide bonds and (2) lipid micelle polymers formed by attaching an amino-terminal lysine to the peptide sequence in question and *then coupling a fatty acid* ***(lipid unit)*** *to* ***both the alpha and epsilon amino groups***" (emphasis added). Here, Sastry et al. teaches the attachment of more than one lipid unit to the peptides with at least one CTL antigenic determinant in question. Thus, the reference teaches compositions comprising "more than one first lipopeptide comprising at least one CTL antigenic determinant and at least one lipid unit."

Therefore, Sastry et al. does teach more than one lipopeptide comprising at least one CTL antigenic determinant and at least one lipid unit. Thus, Sastry et al., and the subsequent combination of references Stuhler et al., Sugimoto et al., Kramer et al., and Shapiro et al. teaches or suggests all of the claim elements.

Therefore, the rejection should be affirmed over this argument in traversal.

Rejection of claim 11 under 103(a) over Stuhler et al., Sastry et al., and Sugimoto et al., and further in view of Kramer et al.

As claim 11 is dependent on claim 1, and as the Appellant provides no additional arguments in traversal of this rejection over those presented above, the rejection stands for the same reasons that the rejection of claim 1 stands.

Rejection of claim 18 under 103(a) under 103(a) over Stuhler et al., Sastry et al., Sugimoto et al., Kramer et al., and further in view of Shapiro et al.

As claim 18 is dependent on claim 1, and as the Appellant provides no additional arguments in traversal of this rejection over those presented above, the rejection stands for the same reasons that the rejection of claim 1 stands.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

M. Franco Salvoza
Patent Examiner, AU 1648

Conferees:

James C. Housel

SPE, Art Unit 1648

JAMES HOUSEL 3/20/06
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Larry Helms

SPE, Art Unit 1643

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER